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Halt-RONIN

Discovering chronic inflammation biomarkers that define key stages in the Healthy-to-NASH (non-alcoholic steatohepatitis) transition to inform early prevention and treatments strategies.

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Halt-RONIN Newsletter March – June 2025

Our project aims to **discover chronic inflammation biomarkers that define critical stages in the Healthy-to-MASLD/MASH transition to inform early prevention and treatment strategies**.

Our newsletters provide our latest news and aim to become a forum for analyzing relevant topics in the field of liver diseases and commenting on some of the most relevant articles published during these four months of the project. Halt-RONIN has reached its 31 months of life. This period has been filled with numerous exciting activities, all of which can be explored in our website: https://halt- ronin.com/news/

On April 8-10 2025, Bilkent and IBG organized a zebrafish workshop at Bilkent University (**Bilkent & IBG Teams HALT-RONIN Data Analysis Workshop**) during which they discussed their progress and data. The information about the meeting can be visited at Bilkent & IBG Meeting.

On April 19th 2025 was celebrated **the World Liver Day**. This day, Leonard Nelson published an article in the **Scotsman newspaper** titled **"You could unknowingly have this dangerous liver disease. Here's what to do"** where he informs about the MASLD, previously called 'fatty liver disease', is a ticking timebomb, affecting 30 to 40 per cent of adults – most of whom don't know they have it. We all know we should be eating more healthily and have a pretty good grasp of why. Cutting down on junk food and turning to more wholesome options in the pursuit of looking or feeling a bit better is nothing new. But what fewer people might realise is that it could heal your liver too.

During these months, we have also organized the **International Seminar Series on Liver Toxicity and Steatotic Liver Disease**. These are taking place every third Wednesday of the month. We have celebrated four seminars:

Date	Speaker	Title
16 April	Volkert Lausche	Organotypic and microphysiological models to study metabolic liver disease
21 May	Magnus Ingelman-Sundberg	An in vivo like liver spheroid system for studies of mechanisms and treatments of steatosis, fibrosis, hepatitis and drug induced hepatoxicity

You can watch the Seminars again here

Javier Cubero
Coordinator of Halt-RONIN
Complutense University, Madrid

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Interesting publications for the consortium:

High inherited risk predicts age-associated increases in fibrosis in patients with MASLD

Background & Aims:

Limited data have prevented routine genetic testing from being integrated into clinical practice in metabolic dysfunction-associated steatotic liver disease (MASLD). We aimed to quantify the effect of genetic variants on changes in fibrosis severity per decade in MASLD.

Methods:

This cross-sectional study included prospectively recruited adults with MASLD aged 18–70 who underwent magnetic resonance elastography (MRE) and genotyping for PNPLA3, TM6SF2, MBOAT7, GCKR, and HSD17B13. A genetic risk score (GRS) was calculated as the sum of established risk alleles in PNPLA3 minus protective variants in HSD17B13 (0=low risk, 1=high risk). We also estimated the polygenic risk score-hepatic fat content (PRS-HFC) and the adjusted version (PRS-5). The primary endpoint was the age-related change in liver stiffness measurement (LSM) on MRE by GRS. Findings were validated using an external cohort from Latin America.

Results:

Among 570 participants, the median age was 57 [49–64] years, 56.8% were women, and 34.2% were Hispanic. Median MRE was 2.4 [2.1–3.0] kPa, and 51% had high GRS. High GRS was independently associated with increased LSM (β=0.28 kPa, 95%CI:0.12–0.44, p=0.001) per 10-year age increase, while the low GRS group showed no significant difference. Similar findings were observed using PRS-HFC and PRS-5. PNPLA3 genotype alone also predicted higher LSM (C/G: β=0.32 kPa, 95%CI:0.02–0.61, p=0.034; G/G: β=0.87 kPa, 95%CI:0.52–1.22, p<0.0001) and G/G genotype was associated with significantly higher LSM by age 44, which was consistent in the validation population.

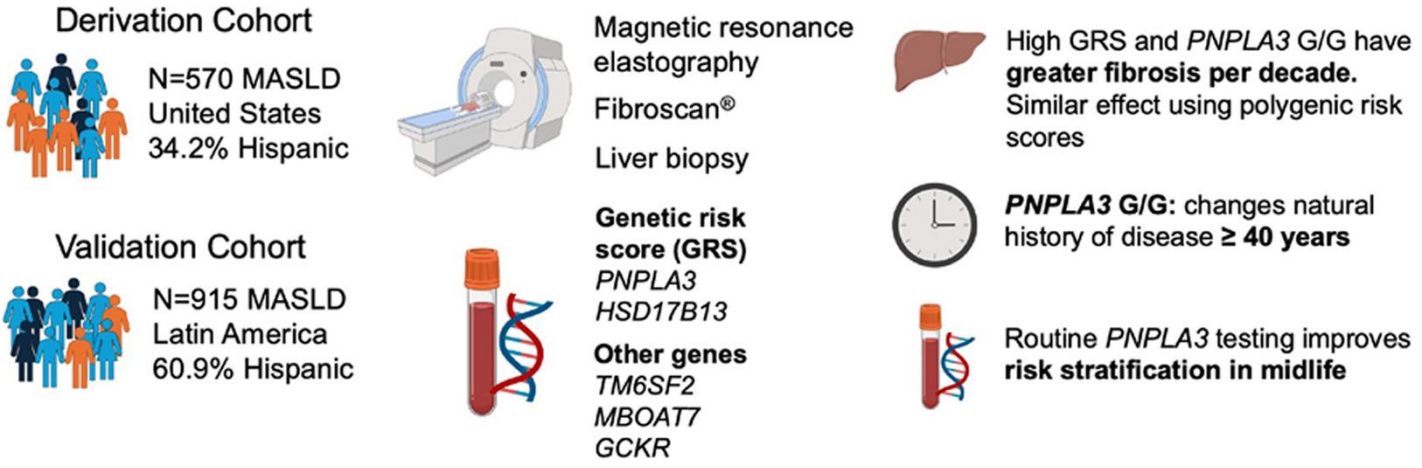
Conclusion:

GRS, PRS-HFC, PRS-5, and PNPLA3 genotypes alone are associated with greater fibrosis per decade, resulting in divergent disease trajectories starting in midlife. Assessing genetic risk in MASLD will identify high-risk patients who require more frequent monitoring.

IMPACT AND IMPLICATIONS:

This study provides granular evidence that genetic predisposition, particularly the PNPLA3 G/G genotype, significantly influences the trajectory of liver fibrosis in patients with metabolic dysfunction-associated steatotic liver disease (MASLD), with a more pronounced impact emerging after the fourth decade of life. These findings highlight the importance of incorporating genetic risk assessment into MASLD management, as it allows for the early identification of high-risk individuals who may benefit from more frequent monitoring and targeted interventions. Given the rising global burden of MASLD, clinicians, researchers, and policymakers should consider integrating genetic stratification into existing risk assessment frameworks to refine screening and surveillance strategies. By optimizing patient selection for non-invasive fibrosis assessment and potential therapeutic interventions, this approach could enhance precision medicine efforts and may improve long-term outcomes.

High Inherited Risk Predicts Age-Associated Increases in Fibrosis in Patients with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)



Access to the original article:

Luis Antonio Díaz, William Alazawi, Saaket Agrawal, Juan Pablo Arab, Marco Arrese, Francisco Idalsoaga, Fernando Javier Barreyro, Adrian Gadano, Sebastián Marciano, Jorge Martínez Morales, Cristiane Villela-Nogueira, Nathalie Leite, Claudia Alves Couto, Rafael Theodoro, Mísia Joyner de Sousa Dias Monteiro, Claudia P Oliveira, Mario G Pessoa, Mario Reis Alvares-da-Silva, Egbert Madamba, Ricki Bettencourt, Lisa M Richards, Amit R Majithia, Amit V Khera, Rohit Loomba, Veeral Ajmera. **High inherited risk predicts age-associated increases in fibrosis in patients with MASLD.** J Hepatol (2025), doi: 10.1016/j.jhep.2025.04.035

Scientific Impact:

According to the WoS, the Impact Factor (IF) of this journal was 26.8 (2023) and it shows a Journal Citation Indicator of 5.97. The Rank (by Journal Citation Indicator) situates this journal in the position 3/143 and the percentile 98.3, that is D1.

Degree of Originality and Innovation: This study presents a highly original and innovative approach by integrating genetic risk assessment into the clinical evaluation of metabolic dysfunction-associated steatotic liver disease (MASLD). Unlike previous research, which has largely relied on environmental and metabolic risk factors, this work pioneers the use of genetic markers—specifically the PNPLA3 genotype and composite genetic risk scores (GRS, PRS-HFC, and PRS-5)—to quantify age-related progression of liver fibrosis using magnetic resonance elastography (MRE), a cutting-edge imaging modality. The study not only demonstrates the predictive power of inherited risk in fibrosis trajectory, but also validates its findings in a large, diverse, biopsy-proven Latin American cohort, enhancing generalizability. Furthermore, the research introduces a practical framework for incorporating genetic data into clinical algorithms, suggesting significant improvements in early detection, risk stratification, and personalized monitoring strategies. By bridging genomics and non-invasive diagnostics, this study significantly advances the field of hepatology and provides a compelling case for the implementation of precision medicine in MASLD management.

Thematic Priority or Challenge Addressed and Contribution to the Scientific Debate:

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This study addresses a major thematic priority in hepatology by tackling the challenge of accurately identifying patients with MASLD who are at high risk of developing advanced liver fibrosis. As MASLD becomes increasingly prevalent worldwide, there is an urgent need for improved risk stratification tools that go beyond conventional metabolic indicators. The study contributes significantly to the scientific debate by providing robust evidence that genetic risk—particularly involving PNPLA3 and polygenic risk scores—can independently predict fibrosis progression over time, even in individuals classified as low-risk using standard clinical tools like FIB-4. These findings challenge current screening paradigms and highlight the limitations of relying solely on metabolic and biochemical markers. By proposing the integration of genetic testing into routine clinical assessment, the study advances the conversation toward a more personalized, genomics-informed approach to MASLD management, and lays the groundwork for updating clinical guidelines to improve early detection and intervention strategies.

Methodological Contribution: This study presents a notable methodological contribution by combining advanced imaging techniques with genetic profiling to assess liver fibrosis risk in MASLD. Specifically, it leverages magnetic resonance elastography (MRE)—a highly accurate, non-invasive modality—to quantify liver stiffness and integrates this with genetic data, including PNPLA3 genotyping and polygenic risk scores (GRS, PRS-HFC, PRS-5). The use of a dichotomized genetic risk framework allows for practical clinical interpretation, while the modeling of age-related fibrosis progression through multivariable regression and spline-based analysis provides granular insight into disease trajectories. The validation of findings in an independent, biopsy-confirmed Latin American cohort further strengthens the study's methodological rigor and external validity. This integrative approach exemplifies a precision medicine framework, demonstrating how genetic and imaging data can be systematically combined to enhance risk stratification and inform personalized monitoring strategies in chronic liver disease.

Publications of the consortium:

Publications			
Title	**Authors**	**Title of the journal or equivalent**	**DOI**
Unraveling MASLD: The Role of Gut Microbiota, Dietary Modulation, and AI-Driven Lifestyle Interventions (Review)	Carolina Jiménez-González, Marta Alonso-Peña, Paula Argos Vélez, Javier Crespo, and Paula Iruzubieta	Nutrients	https://doi.org/10.3390/nu17091580
Trajectory analysis of hepatic stellate cell differentiation reveals metabolic regulation of cell commitment and fibrosis.	Raquel A Martínez García de la Torre, Julia Vallverdú, Zhenqing Xu, et al.	Nat commun	10.1038/s41467-025-56024-4
Atypical and fatal presentation of acute liver failure.	Ana Pérez González, Javier Martín López, Jesús Rivera-Esteban	European Journal of Internal Medicine	https://doi.org/10.1016/j.ejim.2025.05.036
Novel Emerging Mechanisms in Acetaminophen (APAP) Hepatotoxicity (Review).	Alejandro Hionides-Gutierrez, Naroa Goikoetxea-Usandizaga, Carlos Sanz-García, et al.	Liver Int.	10.1111/liv.16167

Communication and Dissemination activities:

Communication Activity Type	**Description**	**Outcome**
Poster	EASL Congress 2025, Amsterdam, Netherlands, 7-10 May. **FRI-146-YI: Genetic polymorphisms associated with idiosyncratic drug-induced liver injury: a systematic review and bioinformatic analysis.** Gonzalo Matilla-Cabello.	Poster communication. Journal of Hepatology 2025 vol. 82(S1) | S70-S858
Poster	EASL Congress 2025, Amsterdam, Netherlands, 7-10 May. **FRI-149: Serum levels of immune checkpoints in drug-induced liver injury and metabolic dysfunction-associated steatotic liver disease**. Juan Pedro Toro Ortiz / Gonzalo Matilla-Cabello.	Poster communication. Journal of Hepatology 2025 vol. 82(S1) | S70-S858
Poster	EASL Congress 2025, Amsterdam, Netherlands, 7-10 May. **FRI-138-YI: Enhanced prediction of drug-induced liver injury in keratinocyte-based high-content single-cell screening integrating machine learning.** Ángela Remesal-Doblado.	Poster communication. (Poster tour; Track hub 7) Journal of Hepatology 2025 vol. 82(S1) | S70-S858
	EASL Congress 2025, Amsterdam, Netherlands, 7-10 May. **FRI-143-YI: Metabolomic profiling to differentiate drug-induced liver injury from other liver diseases using machine learning models.** Daniel E. Di Zeo-Sánchez.	Poster communication. Journal of Hepatology 2025 vol. 82(S1) | S70-S858

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